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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,457	ZHAO ET AL.	
	Examiner	Art Unit	
	ROBERT M. KELLY	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-121* is/are pending in the application.

4a) Of the above claim(s) *1-34 and 52-121* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-51* is/are rejected.

7)☒ Claim(s) *35-51* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/23/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to restriction requirement and amendment of 4/17/08 is entered.

It is noted that Applicant has not amended the claims, and hence, Claims 1-121 are presently pending.

Election/Restrictions

Applicant's election of Group II, Claims 35-51, in the reply filed on 4/17/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-34 and 52-121 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/17/08.

Hence, Claims 35-51 are presently considered.

Claim Objections

Claims 35-51 are objected to because of the following informalities:

Independent Claims 35 and 44 are drawn to "preventing cell death", while the claims do not require any cell death to occur. Hence, it would appear that Applicant is claiming an intension to prevent cell death, which cannot be measured, and hence, the government could not enforce the claim, should the claim issue, as the claim is thwarted simply by stating it was not the intention of the user to prevent cell death. Further, without a commensurate conclusion, the

Artisan would not know if these claims are complete methods. However, as the Artisan would know what is being claimed, the claims are not rejected for lack of clarity.

Claims 36 recites "a bZIP-ATF6 fragment functional, derivatives thereof, and combinations thereof". The punctuation makes the group indeterminate. However, as the Artisan understands what is being claimed, no rejection for lack of clarity is provided. It is recommended that Applicant amend the claim to reflect the punctuation as seen in the presently-similar claim, Claim 45.

Claims 36-43 and 45-51 are objected to for depending from an objected to base claim(s).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 35-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 35-51 are drawn to a generic functional form of ATF6. Particular dependent claims are drawn to full-length form, N-terminal domain forms, bZIP-ATF6 fragments, functional derivatives, covalently modified forms, human ATF6 alpha and beta, and murine ATF6 alpha and beta.

The breadth of these mutant forms are taught in the specification to include a wide variety of mutations, including multiple mutations and deletions, and combinations, as well as covalent modifications.

However, without any demonstration of the inhibition of cell death, either in the Art, or in Applicant's disclosure, the Artisan certainly does not know which regions are required for the ATF6 are required, and further whether any particular modification would have ramifications on the 3 dimensional stereochemistry such that it would preclude cell death inhibition. For example, the Art has long recognized that any particular modification could have long-range structural effects that affect the accessibility or folding of the required structure (Rudinger, et al. (1976) Peptide Hormones, University Park Press, Baltimore, MD., pp. 1-7) (again such structure is not even known as what is required, as the method has not been shown for any cell type).

Therefore, the Artisan could not ascertain that Applicant was in possession of the breadth of generic modifications embraced by the claims.

Claim Rejections - 35 USC § 112

Claims 35-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to inhibiting cell death, which may be caused by mechanism, and may be *in vivo* or *ex vivo*, by administration of an ATF6 protein, as well as a plethora of forms of

ATF6, which may be membrane-bound form, soluble forms, mutated forms, or chemically-modified forms.

The nature of the invention is protein therapy.

The state of the art of protein therapy *in vivo* is highly unpredictable. Torchilin and Lukyanov (2003) Trends in Biochemical Science, 21(11): 259-66, teach that there are many unresolved problems concerning the delivery of proteins and peptides such as rapid elimination from the circulation through renal filtration , enzymatic degradation, uptake by the reticuloendothelial system and accumulation in non-targeted organs and tissues and inefficient cell entry (see Box 1, page 260). Further, with regard to the same *in vivo* therapy and also the structure of the protein administered, Wei Wang (1999) International Journal of Pharmaceutics, 185: 129-88, teaches that protein therapy is unpredictable (page 178, column 2) and involves a number of issues that still need to be resolved: i) functional diversity due to the complexity in size, conformation and charge of a particular protein intended for use as therapeutic pharmaceuticals, ii) Manufacturing and process differences that impact protein heterogeneity, iii) Protein degradation routes, iv) rigid requirement of stable and correct conformation of a protein intended for use as a therapeutic pharmaceuticals, and v) a requirement of compatibility between the protein and the materials used in delivery of the protein.

The state of the Art, while not conflicting with the possibility of ATF6 affecting cell death, fails to provide any evidence that ATF6, or which forms of ATF6 will provide for inhibiting cell death under any specific context. In fact, it appears that at best, ATF6 is associated with unfolded protein response (e.g., Kudo (2003) Nihon Shinkei Seishin Yakurigaku Zasshi, 23(3): 105-09, ABSTRACT ONLY), and hence, those mechanisms that do involve the

unfolded protein response similarly would be expected to unaffected. Still further, in those mechanisms of cell death caused by destruction of various processes or suicide genes are so completely unrelated, it would appear that ATF6 could not be reasonably determined to have any influence on such cell death. Similarly, even within the UPR, other mechanisms are recognized to be involved (e.g., Id.), and hence, simply by affecting a single pathway in the complicated interplay of mechanisms in such cells would similarly not be reasonably expected to work without evidence, or a better understanding of the types of cell death, the mechanisms of each form of cell death, as well as, the interplay of the various mechanisms. Therefore, even if Applicant were to demonstrate a single form of inhibition of cell death, it would appear to be limited to that specific form of cell death which is being inhibited in that particular type of cell.

Applicant's specification broadly describes an invention, and asserts that it has been discovered that ATF6 inhibits cell death.

Applicant provides no examples of any inhibition of any cell death, under any circumstance, and with any cell.

Given the complete dearth of evidence that the methods work, the claims are not substantiated for any breadth at all. The Artisan does not accept mere assertion, but requires reasonable confirmation that the methods would work. In light of the absence of any evidence therefore, the Artisan would have to experiment to determine if/when and with what cell types ATF6 can inhibit cell death, and further determine if any particular form is not working because of the form of ATF6 used, or the administration method, or if the method simply does not work.

Such experimentation is considered undue as it amounts to inventing Applicant's claimed invention for Applicant.

Therefore the claims are not enabled.

Even though facing a complete lack of enablement, because the Artisan would have other reasons to perform the same method steps, certain claims are rejected for being obvious.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 44-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over, alternatively, U.S. Patent No. 6,635,751 or WO 2000/29429, each to Haze, et al.

Because the disclosures are the same, the patent is referred to only.

Haze teaches the administration of ATF6 to a cell, via administration of a plasmid encoding ATF6 (e.g., EXAMPLE 2). Further soluble forms are also taught (e.g., col. 11).

With regard to Claim 46, the ATF6 is human ATF6 (EXAMPLE 3).

With regard to Claims 47-50, mutants comprising, *inter alia*, deletions can be used (e.g., col. 11, paragraph 4), which can obviously be made by covalent modification of the full length protein. Further the deletions would be instantly-obvious to the Artisan that proteolytic processing may be used. Such techniques are well known in the Art (Official Notice).

With regard to Claim 51, water and salts would necessarily be present to allow administration of a functional protein (Official Notice).

As it was well known in the Art that proteins can be administered to cells by injection (Official Notice), it would have been obvious to administer the various ATF6 proteins to cells, instead of using a plasmid to express the protein. The Artisan would have done so to affect the similar tests. Moreover, the Artisan would have had a reasonable expectation of success, as the protein is placed into the cell, which is all that is required.

Lastly, as no demonstration of cell death is provided, it is presumed that any death is prevented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT M. KELLY whose telephone number is (571)272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert M Kelly/
Examiner of Art Unit 1633